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Full dilatation cesarean section: a risk factor for recurrent second-trimester loss and preterm birth

Running title: Full dilatation cesarean and recurrent preterm birth.

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The authors declare no conflicts of interest.

Abstract

Introduction: A previous cesarean section at full dilatation (FDCS) is a risk factor for preterm birth. To provide insight on the risk to subsequent pregnancies, this cohort study compares the outcomes of pregnant women with a previous preterm birth associated either with a prior FDCS

or a prior term vaginal delivery. *Material and methods:* We identified women attending two inner-city preterm surveillance clinics (Guy's and St Thomas Hospital and University College London Hospital, London, UK) who had a spontaneous late miscarriage (14^{+0}–23^{+6} weeks) or sPTB (<37weeks) following a term pregnancy, and then a further pregnancy for analysis. Cases were those with a prior term FDCS, while controls had a prior term vaginal birth; both before the late miscarriage/sPTB. Main outcomes were gestational age at delivery and delivery <30 weeks in the next (third) pregnancy. *Results:* Over the study period 66 women were identified who had a term delivery followed by a late miscarriage or sPTB, and a subsequent pregnancy. Recurrent sPTB <30 weeks was more common in cases compared to controls (12/29, vs 5/37, p=0.02, Fisher's exact test, RR 3.06, 95% CI 1.22-7.71). Median gestation at delivery was significantly lower (249 days (IQR 154, 267) vs 280 days (IQR 259, 280) p<0.001). Eleven women in the FDCS group received vaginal cerclage, five of whom delivered <37 weeks. *Conclusion:* In this cohort study we observed that women with a term FDCS and subsequent late miscarriage/sPTB have a higher risk of recurrent sPTB compared to women whose first term delivery was vaginal.

Keywords:

Cesarean section, preterm birth, cervix, ultrasound, delivery

List of Abbreviations

sPTB	spontaneous preterm birth
sLM	spontaneous late miscarriage
FDCS	full dilatation cesarean section

Key message

Women with a term cesarean at full dilatation, prior to spontaneous late miscarriage/ spontaneous preterm birth have a high risk of recurrent spontaneous preterm birth.

Introduction

Rates of cesarean section, including those at full dilatation (FDCS), are increasing worldwide (1,2). At the same time there has been a decline in operative vaginal delivery, which may be linked to concerns around trauma to the newborn, over-medicalisation and training challenges (3). Cesarean section in the second stage results in greater incidence of morbidity (1,4). Maternal complications include damage to the cervix or high vagina by the uterine incision, as the cervix is drawn into the lower segment (an incidence of 4.4% (5)).

Links between spontaneous late miscarriage (>14 weeks) or spontaneous preterm birth (sPTB) (<37 weeks) following FDCS are beginning to emerge in the literature. A retrospective study at one institution evaluated the effect that a cesarean delivery in one pregnancy had on the risk of sPTB in a subsequent pregnancy (6). The study found that women with a second-stage cesarean delivery had a significantly higher than expected rate of subsequent sPTB (13.5%) compared with both the overall US national sPTB rate (7-8%) and to women who had a first-stage cesarean delivery (2.3%). However, we know little of the course of pregnancies which follow the spontaneous late miscarriage or sPTB, and how best to manage the subsequent pregnancy. The aim of our study was to evaluate outcomes for pregnancies that followed spontaneous late miscarriage /sPTB, where we believe the aetiology of the subsequent early delivery is damage to the cervix/vagina during the term FDCS, compared to women without such damage.

Material and methods

We identified all women presenting to preterm surveillance clinics at two tertiary London hospitals (Guy's and St Thomas NHS Foundation Trust and University College London Hospital NHS Foundation Trust) between April 2012 and November 2016 with a history of spontaneous late miscarriage or sPTB that had been preceded by a term pregnancy. These clinics prospectively collect data for their preterm surveillance clinic databases including contemporaneously obtained outcome. The databases are populated and monitored by research staff trained in Good Clinical Practice. Cases were those with a history of term FDCS before the spontaneous late miscarriage /sPTB while controls were those with a prior term vaginal delivery (spontaneous or assisted). For the purpose of clarification, pregnancies are categorised into A, B and C for each woman, as shown in figure 1.

Women with multiple pregnancies in A, B or C were excluded. Women were excluded if they had a history of sPTB or spontaneous late miscarriage, or previous cervical/pelvic surgery (including cesarean section) prior to pregnancy A. Those with elective or first stage cesarean sections in pregnancy A were excluded. Term deliveries prior to pregnancy A and first trimester miscarriages (<14 weeks) or terminations of pregnancy (any gestation) were omitted for the purposes of analysis.

Pregnancy B was defined as the first subsequent spontaneous late miscarriage/sPTB following the term delivery. The main outcomes of interest were gestational age at delivery and delivery < 30 weeks (primary endpoint) in pregnancy C (defined as the next pregnancy following pregnancy B). Premature births less than 30 weeks have recently been identified as of particular significance by the UK National Institute for Health and Care Excellence (NICE) who advise admission, steroids and tocolysis without diagnostic testing for any women in threatened preterm labour below this gestation (7). We also reported preterm birth rates prior to 34 and 37 weeks in view of their clinical relevance (secondary endpoints).

At the clinics, pregnancies are managed according to prespecified protocols using regular ultrasound transvaginal cervical length measurement to guide decisions about preventive therapy such as cervical cerclage. Vaginal cervical cerclage is offered to women who are found to have a short cervical length (<25mm) on ultrasound surveillance. Transabdominal cerclage is usually reserved for those who have had a failed vaginal cerclage previously, defined as delivery before 28 weeks despite having a vaginal cerclage.

Variables collected included maternal age, ethnicity, parity, body mass index and smoking history. As secondary outcome measures, we collected data on timings and nature of interventions aimed to prevent spontaneous late miscarriage and sPTB, such as cerclage (history-indicated/ultrasound-indicated/rescue/transabdominal), progesterone or Arabin pessary in pregnancy C.

Statistical analysis was performed using Stata software Version 14.1 (StataCorp, College Station, Texas). Data was skewed so median gestations were compared with a Wilcoxon rank-sum test and confidence intervals (8). Time to delivery was displayed using a Kaplan-Meier plot. Fisher's exact test was used to compare percentages (sPTB < 30 weeks).

Ethical approval

The study was conducted according to the principles set forth in the Helsinki Declaration of 1975, as revised in 2013. We obtained a waiver of Institutional Review Board approval from the two relevant NHS Health Research Authorities who confirmed that the study was classified as service evaluation and therefore Research Ethics Committee review or Health Research Authority approval was not necessary. Reporting of this study was conducted in accordance with the STROBE Statement.

Results

Sixty-six women with a spontaneous late miscarriage /sPTB following a term delivery were identified, with a total of 198 pregnancies for analysis. There were 29 women with a prior FDCS who had completed a further pregnancy between April 2012 and November 2016. The remaining 37 who had a prior term vaginal delivery were treated as controls. Cases and controls had similar baseline characteristics (Table 1). There were 6 reported cases of past or present history of Group B Streptococcus in the cases compared to three in the control group. Only one woman (control) reported previous bacterial vaginosis. Three women in the cases reported a history of recurrent urinary tract infections, and one of the controls. No women reported intimate partner violence despite routine screening in both clinics.

Median gestation was significantly lower (35^{+4} weeks (interquartile range 22^{+0}, 38^{+1}) vs 40^{+0} weeks days (interquartile range 37^{+0}, 40^{+0}) $p<0.001$) in the cases compared to controls. For women with a prior term FDCS and subsequent late miscarriage/sPTB in pregnancy A and B respectively, the relative risk of recurrent sPTB less than 30 weeks in pregnancy C was 3.06 (95% CI 1.22-7.71) compared to women with prior term vaginal delivery and subsequent late miscarriage /sPTB (12/29 vs 5/37 p=0.02, Fisher's exact test). The absolute risk of recurrent sPTB in pregnancy C for women with a previous term FDCS was 28% (95% CI 7%-49%). The

incidence of sPTB less than 34 weeks was 12/29 vs 5/37 (p=0.02, Fisher's exact test), and the incidence before 37 weeks was 16/29 vs 7/37 (p=0.0038 Fisher's exact test). This was in spite of a higher rate of intervention (17/29 vs 6/37 received intervention in cases compared to controls). Kaplan-Meier "Survival" estimates depict the proportion of women undelivered at each gestational week according for cases and controls (figure 2)

In order to exclude possible effects of intervention on outcome, we compared sPTB rates in women without intervention in each group. In women who received no intervention in pregnancy C, cases had a higher rate of sPTB relative to controls (10/12 vs 4/34, p<0.0001 Fisher's exact test). A description of the interventions received in pregnancy C and their sPTB rates are provided in Table 2.

Discussion

Caesarean section at full dilatation is increasingly common. However counselling women who have a FDCS followed by a late miscarriage or sPTB is challenging because the incidence of sPTB following any term delivery is low (9). This unique study analyses the subsequent pregnancies of this group. It demonstrates that women with a prior history of term FDCS and subsequent late miscarriage/sPTB have a threefold increased relative risk of recurrent sPTB compared to those women with a history of term vaginal delivery and subsequent late miscarriage/sPTB.

In this study, management decisions whilst guided by ultrasound surveillance, varied according to clinician preference. Conservative management in pregnancies that followed late miscarriage/sPTB was associated with higher recurrence of sPTB in women with a prior history of FDCS compared to a vaginal delivery. More women with a history of term FDCS received an intervention than those delivering vaginally at term, but in spite of this, their overall outcomes were worse. In this small cohort, transabdominal cerclage appeared the most effective treatment but a larger sample would be required to demonstrate whether this is a true finding.

The high recurrent sPTB risk is consistent with a previously observed 6-fold increased odds of having an sPTB following a FDCS, relative to a first stage cesarean (adjusted odds ratio 5.8; 95% CI 1.08-30.8; P =0.04) (6). Alternative physiological mechanisms that result in premature birth may account for the excess risk. In three cases an anterior cervical defect was clearly seen on ultrasound. This is likely to be associated with incision at the time of cesarean section, which may be inadvertently too low (figure 2). It is worth noting however that a caesarean section defect was not systematically looked for in all cases, and the rate of anterior cervical defects may be higher than this. Whilst cervical defects may not be apparent in every case, the optimum management of this subset of women needs to be established. If transabdominal cerclage supports the cervix above a defect caused by a low FDCS incision, it may provide a more logical rationale for this intervention and offer the best chance of a term pregnancy for these women. A potential increase in gestation at birth, however, needs to be balanced against the risks of major surgery.

Spontaneous preterm birth or late miscarriage following term pregnancies is relatively rare and this is a unique cohort of 66 women with longitudinal data. Another strength of the study is that the data is from pregnancies that were followed in two clinics sharing common protocols for management of recurrent sPTB.

The sample size and detailed information were restricted by the need to examine three pregnancies in each woman, the first two of which may have occurred over many years and in different hospitals or countries. For example, data on the indication for the FDCS and whether an instrumental delivery was attempted, might further the understanding of the sPTB recurrence risk. Data on serial cervical length and fetal fibronectin values for each pregnancy might have enabled us to make more specific recommendations regarding management of future pregnancies in these women. Increasing awareness of the risk of recurrent late miscarriage/sPTB following FDCS is likely to facilitate future data collection. The low numbers of diverse interventions women received mean that whilst trends were observed, statistical significance was not reached on data that could suggest best management strategies.

There may be a degree of selection bias in the cases as we have only recently become aware of FDCS as a risk factor, so the details of a preceding caesarean section may not have been actively sought for all women presenting at these clinics. However cases we have selected genuinely have this history. To minimise bias and because preterm birth after term delivery is rare, we selected all cases and controls in the timeframe, rather than matching. The baseline characteristics are comparable.

We believe our results are generalisable as these cases were referred by many units to these specialist services. However, as the insult is likely to be iatrogenic, obstetric practice could influence risk (i.e. threshold of when to do cesareans and technique of incision), so these findings should also be confirmed in other clinical settings (e.g. outside the UK).

Recurrent spontaneous late miscarriage or sPTB has a major impact for a woman and her family and our findings are therefore relevant to all women who are delivered by cesarean at full dilatation and clinicians who are evaluating management options in the second stage. The recurrence risk and management challenges we have demonstrated, highlight the need for early specialist referral and the inadequacy of a conservative approach. Given the persistent risk that a FDCS poses to a small but increasing number of women, future trials may explore preventative strategies at the time of FDCS, such as high incisions in the lower segment, and best management of subsequent pregnancies, which may include transabdominal cervical cerclage in the presence of an anterior cervical defect. Observational imaging and biomarker studies may also help determine the aetiology and optimum management of this problem.

Conclusion

Spontaneous preterm birth and late miscarriage following FDCS are associated with poor outcomes and these women require specialist surveillance and management in subsequent pregnancies. Women should be counselled regarding these implications following cesarean delivery in the second stage. Clinicians should be aware of FDCS as a risk factor.

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Legends

Figure 1. Description of analysed pregnancies.

Figure 2. Kaplan-Meier "Survival" estimates depicting the proportion of women undelivered in Pregnancy C at each gestational week according for cases and controls. sPTB, spontaneous preterm birth.

Table 1. Baseline characteristics of cases and controls.

Table 2: Interventions and outcome in pregnancy C (pregnancy following spontaneous late miscarriage/ spontaneous preterm birth).

Table 1. Baseline characteristics of cases and controls.

Characteristic	Pregnancy C: Index Pregnancy	
	CASES[1] n=29 (%)	CONTROLS [2] n=37 (%)
Mean age (years) (SD)	33 (4.1)	36 (5.3)
Mean gestation pregnancy B (weeks) (+/-SD)	21 (6.2)	22 (5.7)
Median gestation pregnancy B (IQR)	20 (18.0, 23.0)	20 (18.0, 25.0)
Ethnicity (%) *Black* *White* *Other (Asian/Middle-Eastern)*	 8 (28) 18 (62) 3 (10)	 13 (35) 22 (59) 2 (6)
Reported smoking history Current Ex-smoker Never	 0 (0) 3 (12) 23 (88)	 9 (24) 0 28 (76)
Mean Body Mass Index BMI < 20	30.1 0	29.1 3

[1] Cases: term full dilatation cesarean section prior to spontaneous late miscarriage or spontaneous preterm birth.

[2] Controls: term vaginal delivery prior to spontaneous late miscarriage or spontaneous preterm birth.

SD, standard deviation; IQR, interquartile range; BMI, body mass index.

Table 2: Interventions and outcome in pregnancy C (pregnancy following spontaneous late miscarriage/ spontaneous preterm birth).

	CASES (term FDCS prior to sLM or sPTB) n= 29		CONTROLS (term VD prior to sLM or sPTB) n=37	
Pregnancy C Management	No. of women receiving this intervention	No. of women delivered <37 weeks	No. of women receiving this intervention	No. of women delivered <37 weeks
No intervention[a]	12	10	31	4
History indicated cerclage	7	3	2	2
Ultrasound indicated cerclage	2	0	2	1
Rescue cerclage	2	2	2	0
Transabdominal cerclage	4	1	0	0
Arabin pessary	1	0	0	0
Progesterone	1	0	0	0

[a]$p<0.0001$ (Fisher's exact test)

FDCS, full dilatation cesarean section; sLM, spontaneous late miscarriage; sPTB, spontaneous preterm birth; VD, vaginal delivery.

Figure 1: Description of analysed pregnancies

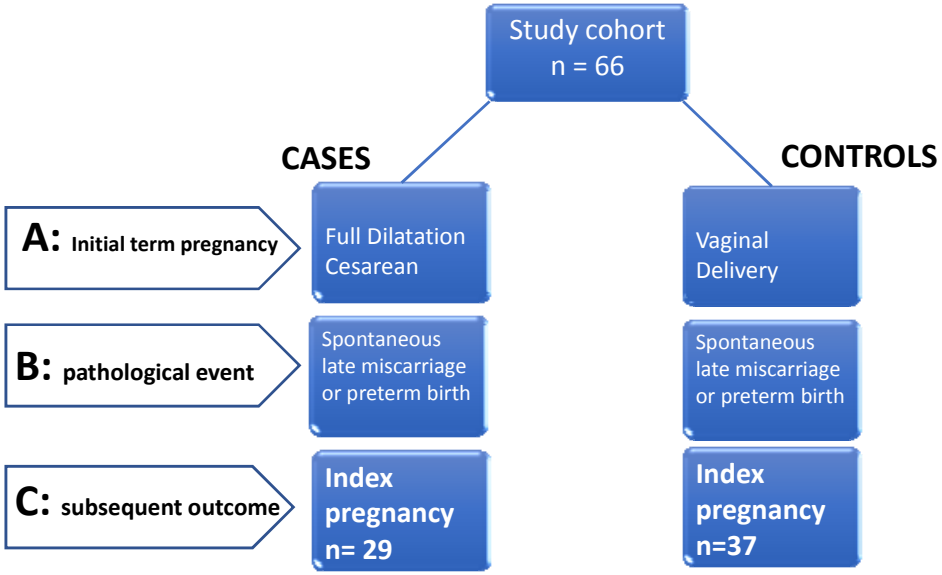

Figure 2: Kaplan-Meier "Survival" estimates depicting the proportion of women undelivered in Pregnancy C at each gestational week according for cases and controls